Colin Bouwer: Professor of Psychiatry and murderer

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I first heard of Colin Bouwer on 4 March 2001 when I received an email from Detective Sergeant Brett Roberts of Dunedin, New Zealand. The story he told was a fascinating one. Nine months earlier he had arrested Colin Bouwer, who was Head of the Department of Psychiatry in Otago Medical School in Dunedin, on a charge of murdering his wife. During the three months preceding his wife's death Colin had written false prescriptions for a long list of drugs, including insulin, which would not ordinarily be prescribed by a psychiatrist except possibly for his own use. The police obtained a search warrant and found on Colin's computer a number of emails that suggested he had injected his wife with insulin some 7–12 hours before her death. He had also emailed a number of international hypoglycaemia experts claiming to be a forensic psychiatrist dealing with a 47-year-old woman who had died in her sleep. The questions he posed related to the injection of insulin or the ingestion of sulphonylurea drugs (medicines used to treat diabetes) and the likely problems of establishing them as a cause of hypoglycaemia.

I was not on Colin Bouwer's email list, nor did I know anyone who was. The police had, however, come across my name as the author of a paper entitled 'Murder by insulin' that I had recently published in the *Medico-Legal Journal*.[1] They wondered whether Colin had phoned or written to me. Just in case I might dismiss his email as a hoax, Sergeant Roberts gave me his telephone number, although his email address – @police.govt.nz – was a bit of a giveaway. Nevertheless, to be on the safe side, I did phone him as well as replying to his email to say that I had never heard of Dr. Bouwer and that he had never been in touch.

I thought that was the end of it until I received a telephone call from Anne Stevens, a barrister, on 1 May 2001. She and leading counsel David More were defending Colin Bouwer on a charge of killing his wife by injecting her with insulin after weeks of trying to do so with sulphonylureas. They wanted me to review the evidence and express an opinion.

I agreed to do so and promptly received a mass of clinical notes relating to Annette Bouwer's last illness during November and December 1999 and her death on 5 January 2000. Anne Stevens also sent me witness statements by a number of local experts who had been consulted by the police. By the end of May I had received a letter from David More telling me that the current defence position was that Annette had suffered from hypoglycaemia due to an insulinoma (an insulin-secreting tumour) and that it had been missed both at operation and at postmortem. An alternative explanation was that she had committed suicide with drugs her husband had stockpiled for his own suicide when it became evident to her that her doctors could do no more than they already had done to alleviate her ongoing suffering.

Case history

The story of Colin and Annette Bouwer began at around 6.30 am on the morning of 20 November 1999 when an ambulance arrived at the Bouwer household.

Colin had summoned the ambulance when he found Annette lying comatose on her bed. The crew confirmed that Annette was in a deep coma (Glasgow Coma Score [GCS] 3) and measured her blood sugar with a simple point-of-care device (POCD). It was 1.3 mmol/L – easily low enough to account for her coma. They immediately gave her some glucose-containing gel by mouth and five minutes later, when this failed to have any effect, injected her with 1 mg of glucagon.

Thirty minutes later, when the ambulance arrived at the Accident and Emergency Department of Dunedin Hospital, Annette's blood sugar level had risen to 5.5 mmol/L, indicating that the glucagon had done its job and overcome her hypoglycaemia. The first doctors to see her rated her GCS as 15, which is as good as it gets, and showed that she was fully conscious. She was mildly hypothermic (temperature of 34.7°C),

Figure 1
Colin Bouwer

which is common in people who have been hypoglycaemic for any length of time.

By 7.45 am, Annette's blood sugar level had again fallen to 2.6 mmol/ L and, though still fully conscious, she was given a further 25 g of glucose intravenously as a 50% solution. A 5% intravenous glucose drip was also set up. This combination of treatments led to her blood sugar level 10 minutes later being 14.5 mmol/L, which is rather high, and to her urine containing large amounts of glucose.

Annette told the doctors that her health had been declining over the previous three weeks and that she had been both very thirsty and very hungry, particularly at night. She had also gained a lot of weight. Other symptoms were an inability to concentrate, blurring of vision, excessive sweating at night and episodes of poor balance. She denied drinking alcohol to excess or taking any medicines.

Annette was given glucose both by mouth and intravenously and her blood sugar was monitored by a POCD throughout the morning. No formal testing beyond that undertaken on her admission was done in the laboratory until noon, when her blood sugar level had again sunk to 1.2 mmol/L. Although she was still apparently symptom-free, a venous sample of blood was collected and sent to the laboratory to be assayed for glucose, insulin, C-peptide and growth hormone.

For the rest of the day of admission she ate normal meals and continued to receive small doses of glucose intravenously. Despite this, she persistently had low blood sugar levels within the range 3–3.5 mmol/L. The rate of glucose infusion was increased to 20 g/hr but even this failed to raise her blood glucose level to normal. Eventually, at 12.45 am on 21 November, almost 18 hours after she was found comatose, a sample of venous blood was collected and sent to the laboratory for testing for sulphonylureas. Her blood glucose was by this time still only 4–5 mmol/L despite the large amount of glucose she had received.

Analysis of this sample of blood failed to show the presence of any of the five sulphonylurea drugs (tolbutamide, chlorpropamide, glibenclamide, gliclazide and glipizide) available in New Zealand at the time. Surprisingly, no insulin or C-peptide measurements were made on this sample.

Annette continued to receive intravenous glucose at the rate of 15 g/hr during the whole of 21 November, much or all of 22 November and seemingly part of 23 November. At no time was her blood sugar greater than about 8 mmol/L and for most of the time it was in the range 4–5 mmol/L (i.e. low normal). Her average blood glucose level did not change significantly after the intravenous glucose infusion was stopped. On 23 November, presumably in the hope of detecting an insulinoma of the pancreas, she underwent a computed tomography (CT) scan of her abdomen, which revealed nothing abnormal, not unexpectedly since it rarely does in cases of insulinoma.

Annette was discharged on 24 November with a provisional diagnosis of hypoglycaemia due to an unknown cause, probably an insulinoma. A follow-up appointment was made for her to see Dr Andrew Bowers, the consultant physician who was looking after her, two weeks later, by when he would have received the insulin and C-peptide results from the laboratory in another hospital to which they had been sent for analysis.

Just before she was discharged, Annette was tested to rule out adrenocortical insufficiency – a rare but important glandular cause of hypoglycaemia, in which plasma insulin and C-peptide levels are both low. In Annette's case, the concentrations of insulin and C-peptide were both inappropriately high for someone whose blood glucose concentration was low. This combination occurs, for all practical purposes, in only three situations: a benign tumour of the insulin-secreting tissues of the pancreas (i.e. an insulinoma); a condition

resembling it in which all of the islets are affected, though not necessarily morphologically, called non-islet cell hyperinsulinaemic hypoglycaemia (NICHH); and poisoning with one of the sulphonylurea drugs. Sulphonylureas had ostensibly been ruled out by the test carried out 16 hours after she had first come into the hospital and while she still required intravenous glucose to prevent her becoming hypoglycaemic. This left only an insulinoma, or the even rarer condition NICHH, to consider.

Blood tests made by Annette using the glucose meter she had been given on discharge showed that on many occasions during the days following discharge, her blood glucose level fell below 2.5 mmol/L (the level that defines hypoglycaemia) and was sometimes so low as to be incompatible with normal consciousness, suggesting some inaccuracy in making the measurements. At no time, even after meals, did her blood glucose level rise above about 6 mmol/L. This is decidedly abnormal.

Annette was back in hospital on 29 November. The ambulance crew had again been called by her husband at 6 am, and arrived around 6.30 am to find her comatose with a GCS of 3. The immediate administration of glucagon led her to recover sufficiently to swallow some Instagel, a glucose paste which can be smeared on the inside of the mouth. By 7.00 am, her GCS was 14, which is virtually normal, and, on her arrival at the A&E Department, her blood glucose was 4.6 mmol/L, which is normal but low for someone who had been given 1 mg of glucagon and glucose by mouth just 40 minutes earlier.

Dr Mark Reeves, the first doctor to examine Annette, noted that she was pale and sweaty, and slightly hypothermic with a temperature on admission of 35°C. Her blood sugar level was already normal, 6.1 mmol/L, in response to the glucagon she had been given. Dr Reeves collected some venous blood and sent it to the laboratory for analysis. In the laboratory Annette's blood glucose level was recorded as 7.4 mmol/L. The plasma insulin level was 299 pmol/L, which is quite appropriate for a blood glucose level of 7.4 mmol/L. Extraordinarily, the plasma C-peptide was not measured on this sample of blood, but might reasonably have been expected also to be normal.

A further venous blood sample, collected at 9.20 am, after Annette had been taken to the wards, was analysed and contained C-peptide at a concentration of 1390 pmol/L, which is high but difficult to interpret since the blood glucose and insulin concentrations were not measured on that particular sample.

Soon after admission, Annette was given an intravenous infusion of glucose at the relatively rapid rate of 15 g/hour. This was continued with the addition, from 2 December, of diazoxide, a drug that blocks the secretion of insulin by the pancreas, especially when it is due to sulphonylurea stimulation. She remained on diazoxide until 10 December, when the dose was temporarily halved before being restored to its original level because of her continuing low blood glucose levels.

Throughout this time, Annette's blood glucose levels were monitored by frequent POCD measurements and were consistently low, often falling below the critical level for diagnosis of hypoglycaemia of 2.5 mmol/L, but no further insulin, C-peptide or proinsulin measurements were made.

On 1 December, before she was given diazoxide and after discussion with the radiologist, Dr Morrison, Annette had undergone an arterial (calcium) stimulation test. This is a very sophisticated test available only in leading medical institutions even today, let alone in 1999, and is designed to localize an insulin-secreting tumour of the pancreas, which Annette was strongly suspected of suffering from. In his case notes Dr Morrison described the test as 'routine: no problem'. His report issued on 2 December explained the procedure and said that, 'Following injection [of calcium gluconate] into the gastroduodenal artery the blood sugar level dropped from 6 to 1.6 mmol/L'. This suggests that the calcium injection had caused a large release of insulin, sufficient in fact to lower the blood glucose concentration very substantially, which would not have been expected if the insulin-secreting beta-cells in Annette's pancreas were normal.

In the calcium infusion test, blood samples are collected from the hepatic vein through a very fine plastic tube, which is inserted into a vein in the groin and threaded up into the hepatic vein under radiological control. This, like the manoeuvre required to inject calcium into the various arteries supplying the pancreas with blood, is complicated and depends upon the skills of an interventional radiologist. At the time of Annette's test there were very few units in the world capable of doing it. It is ironic, therefore, that blood collected during the test had to be sent away to a laboratory in Canterbury, New Zealand, for insulin analysis, which by 1999 was considered routine in many hospital laboratories. To their credit, the

Canterbury Laboratory treated the samples as urgent and reported the results almost by return.

The analyses showed that plasma insulin levels in the hepatic vein did not rise after calcium was injected into the artery that supplies the liver with blood, which was only to be expected. What was not expected was that the concentration of insulin in the hepatic vein rose at least twofold after injection of calcium into each of the arteries supplying the pancreas with blood. None of the doctors consulted had ever seen or even heard of a similar result before, and mistakenly interpreted it as indicating an insulin-secreting tumour in the tail of the pancreas. Typically, however, in this condition, a rise in plasma insulin occurs only after the artery supplying the tail of the pancreas has been injected and not when either of the other two arteries supplying the rest of the pancreas are injected.

Annette's diazoxide therapy began the next day. Even though she was receiving large doses of glucose intravenously, eating normally and getting diazoxide therapy, Annette's blood glucose level remained low during the whole of her remaining time in hospital.

On 6 December, Dr Bowers discussed with Annette the possible need for surgical removal of the insulin-secreting tumour of the pancreas she was believed to have or, if they failed to find one, the effects of partial removal of the pancreas. Dr Bowers, Dr Patrick Manning, the consultant endocrinologist, and Dr Thomas Elliott, a consultant surgeon, having agreed that the results were most consistent with an insulinoma in the tail of the pancreas, scheduled her for surgery on Monday 13 December. They appeared not to be aware of just how uncharacteristic of a solitary insulinoma the calcium infusion test result was. The anaesthetist consulted by Dr Bowers suggested that for 24 hours prior to surgery Annette should be treated with octreotide (Sandostatin) rather than diazoxide. Octreotide is far more potent than diazoxide for inhibiting insulin secretion. It suffers from the disadvantage that it can only be administered by injection, which limits its usefulness for the treatment of hypoglycaemia caused by an insulin-secreting tumour.

Later that same day Dr Manning told Dr Bowers of his concerns about the results of the calcium stimulation test, which were somewhat unusual. He had discussed them with Professor Halliday of Auckland, an authority on this still-novel procedure, who had agreed that Dr Elliott, the surgeon, should remove two-thirds or more of the pancreas if he could not find a solitary tumour. This is, in fact, what occurred.

Dr Han-Seung Yoon, the hospital pathologist, examined stained slices of the pancreas with a microscope but found no evidence of tumour in it or in the lymph nodes Dr Elliott had removed. He described the small nodule attached to the small intestine, which Dr Elliott had also removed, as a 'carcinoid tumour consistent with an insulinoma'. Insulinomas can, extremely rarely, develop outside the pancreas, so here was a possible explanation for Annette's hypoglycaemia. Subsequent examination using a more sophisticated immunostaining technique, however, showed that this particular carcinoid did not contain or secrete insulin. It was therefore not an insulinoma and the mystery remained unsolved.

Because she had not become hypoglycaemic during a fast test on 23 December, Annette was discharged home on Christmas Eve. She was instructed to continue monitoring her blood glucose level by pricking her finger and using the POCD and to report back to the hospital if her blood sugar was low even if she did not have symptoms.

Annette was not prescribed diazoxide or octreotide but went home with a prescription for Creon, a pancreatic enzyme (pancreatin) preparation to assist her digestion, paracetamol for pain relief and penicillin to prevent the surgical wound becoming infected. It is unclear just how much her husband Colin was involved in the discharge process and the discussions that took place on what should be done if she did become hypoglycaemic at home.

On 2 January 2000 Colin contacted Dr Manning, who was standing in for Dr Bowers, to say that his wife was not well and that her blood sugar levels were consistently low. He said they were generally between 2.5 and 3.0 mmol/L and that Annette had brief periods of slurred speech and unsteadiness on her feet. He was not unduly concerned, however, because he said that Annette had been told that a blood glucose level as low as 2.5 mmol/L did occasionally occur in healthy individuals – though who, if anyone, would have given such bad advice was never revealed. On the afternoon of 4 January Colin collected a venous blood sample from Annette and took it to the hospital laboratory for glucose, insulin and C-peptide assay. The blood glucose level was so low, 1.7 mmol/L, that after checking it for accuracy the analyst phoned out the result to the phone number given on the request form as any competent laboratory worker would. He later testified that the specimen he had received was grossly haemolysed and quite unsuitable for the insulin and C-peptide assays that had also been requested. He

asked that a further sample be sent, but it never came, as by next morning, Annette was dead. Consequently the exact cause of her hypoglycaemia at 4.30 pm on 4 January was never established and could only be inferred from what was found at postmortem.

Colin found Annette dead in bed on the morning of 5 January. He immediately phoned Dr Bowers, who called round to the house straight away. He confirmed that Annette was dead and that she had apparently vomited. He observed traces of Instagel around her lips, suggesting that someone had tried to resuscitate her, and expressed his willingness to sign a death certificate to the effect that she had died from hypoglycaemia, probably from an insulinoma that had been missed and therefore left behind after the operation. Before doing so, however, and because he had not seen Annette for a couple of weeks, he spoke to the coroner, who indicated that he would be satisfied with just a regular hospital postmortem rather than a forensic one.

At this stage everyone assumed that, despite their best efforts, the surgeons had failed to find a small insulinoma that would undoubtedly be found at postmortem. Dr Yoon, the Consultant Pathologist in Dunedin Hospital and Associate Professor in the University of Otago, carried out an autopsy on the morning of Annette's death. He described the body as that of a middle-aged woman who bore a large bruise at the flexure of the left elbow that contained five needle marks, presumably where Colin had collected blood from Annette the previous day. There was a further needle mark in the flexure of the right elbow.

Her right lung weighed almost twice as much as the left and showed early changes suggesting that Annette had suffered pneumonia from breathing in something noxious, probably the vomit noticed by Dr Bowers. The pericardial space contained 88 mL of fluid. The heart itself appeared to be normal to the naked eye, but examination in the laboratory revealed focal muscle degeneration and patchy inflammation of both the lining of the heart and the heart muscle itself. The liver showed changes consistent with heart failure, but apart from fat necrosis surrounding the pancreas, which was probably due to her recent surgery, Dr Yoon found nothing else abnormal. He described the brain, which weighed 1386 g, as 'normal' but did not preserve it intact for later neuropathological examination, as perhaps he should have done in someone who was purported to have died from hypoglycaemia. He found no evidence of the ventriculo-peritoneal shunt that Colin had told the doctors Annette had been given a few years earlier and which, it was later discovered, was simply an invention of Colin's – it subsequently emerged that Colin was a fantasist and liar on a grand scale.

In the course of the autopsy Dr Yoon collected blood and urine for analysis. He also took a sample of vitreous humour (liquid from the eyeball) to measure its glucose concentration. His initial conclusion, made on the basis of his postmortem examination of the body and laboratory examination of the tissues he had removed, was that Annette had neither an insulinoma nor pancreatic beta-cell hyperplasia. He concluded that the abnormalities he had found in Annette's body were most likely due to insulin overdose and not to any abnormality of her own insulin-secreting cells, which he described as normal.

Later, after the opinions of more experienced endocrine pathologists had been sought, Dr Yoon changed his mind and agreed with the opinion expressed by Professor Ian Holdaway, an eminent endocrinologist from Auckland, that Annette's pancreas showed evidence of islet hyperplasia. This is a condition recognized by examination under the microscope, in which the islets of Langerhans are uniformly enlarged. Whether Annette did or did not have islet hyperplasia and the differing interpretations put on it figured prominently in the evidence the experts called by the prosecution and by the defence gave on the witness stand.

Whilst in hospital Annette had alleged that she was being poisoned, and so by the time Dr Yoon had finished the naked-eye autopsy and found nothing to account for her death, he decided to discuss the matter with the police. Later that day the police arranged for a forensic postmortem examination to be conducted by John Blennerhassett, Emeritus Professor of Pathology in the University of Otago in Dunedin, on the afternoon of 7 January 2000. During this further examination Professor Blennerhassett found a small benign tumour, 15 mm in diameter, in the tissues in the middle of the chest that had previously been overlooked. He described it as a thymoma. Immuno-histochemical examination confirmed that it, like the small carcinoid removed at operation, did not contain or secrete insulin.

Professor Blennerhassett also noted that Annette's skull was normal and did not contain the holes in it that were required had she really had the ventricular shunt that Colin claimed she did. Professor Blennerhassett, like Dr Yoon, found no evidence of pancreatic islet cell hyperplasia.

Blood samples collected at autopsy by both Dr Yoon and Professor Blennerhassett were sent to Dr Heenan, a toxicologist who, using state-of-the-art technology far more sophisticated than that used on Annette's blood whilst she was still alive, found a host of drugs that should not have been there – most of them not ordinarily available except on prescription.

Amongst the drugs found were two different sulphonylureas, glibenclamide and glipizide, both at concentrations within or only slightly above those normally found in diabetic patients treated with them. Metformin, another antidiabetic, was also present at an unbelievably high concentration – more than five times the maximum level expected in someone receiving legitimate treatment. Also present was the tranquillizer clonazepam and its major breakdown product, 7-aminoclonazepam. They were present in all of the blood samples sent for analysis by both pathologists and were again several times higher than the therapeutic level, but for some mysterious reasons their concentrations were very different in the samples collected by Dr Yoon and Professor Blennerhassett.

An antidepressant drug, citalopram, was also found in the postmortem blood samples. It was subsequently found in the sample of blood that Colin had collected from Annette on the afternoon just before her death, as were glibenclamide and glipizide, though at lower and higher concentrations, respectively, than in the postmortem blood. This is not altogether surprising, as it is now well known that drug levels in postmortem blood are often a very poor indicator of their concentration in blood during life. Since the sample of blood Colin had collected also had a low blood glucose concentration, it is impossible to escape the conclusion that this was due at least in part, and probably entirely, to the two sulphonylurea drugs acting in concert.

Examination of the stomach contents removed at autopsy showed traces of glibenclamide, glipizide and citalopram. Their concentrations were consistent with those in the blood itself, suggesting that almost all the dose had been absorbed by the time Annette had died. In other words, at least several hours had elapsed between the times she had last taken the drugs and her death.

By now there could be little doubt that Annette had not died naturally, as Dr Bowers had originally assumed, but was poisoned. The search was on for who was responsible. Had she taken the drugs deliberately because life had become intolerable as a result of the hypoglycaemia that the doctors seemed quite unable to do anything about? Or had Colin systematically poisoned her over the last month or so of her life? The police started an investigation, and nine months later Colin was on trial on a charge of murdering his wife.

The investigation

The police investigation soon established a possible motive. Colin was in the midst of a passionate love affair with Dr Anne Walshe, one of his colleagues. She had become Colin's lover following their attendance at a conference in Copenhagen, just a few weeks before he began writing prescriptions for fictitious patients. The first prescription for glibenclamide was dispensed on 16 November, four days before Annette's first hypoglycaemic coma. The last of no less than 11 prescriptions traced to Colin was dispensed at 4 pm on 4 January 2000, just 30 minutes before he took blood from Annette for analysis and sent it to the laboratory. That prescription was the only one to include insulin. There was no evidence that Anne Walshe was involved with, or knew about, Colin's prescription writing or his subsequent behaviour.

Among the things the police discovered in the Bouwer household was a hoard of antidiabetic drugs, including glibenclamide, glipizide and metformin, which would not ordinarily be expected in a psychiatrist's home unless he or a member of his family suffered from type 2 diabetes. Even so, the quantities found were truly enormous by any standards and represented the fruits of the prescriptions that Bouwer had made out in the name of fictitious patients during the two months preceding Annette's death. Much was made of the fact that Colin had, when he was first asked about it soon after Annette's first admission to hospital, vehemently denied the possibility that she could have had access to sulphonylureas. To back up his assertion, he claimed to have searched the house and found none.

Research into Colin's background revealed him to be a fantasist of Baron Münchausen proportions. He described himself as having been tortured by the secret police because of his association with the African National Congress (ANC) during the apartheid regime. As a result, he said, he had lost a testicle as well as being subjected to electrical torture. This was untrue, but there was documentary evidence that the South African Health Professions Council had proclaimed him an impaired doctor because of his addiction to pethidine prior to his departure for New Zealand. His credibility as an

upright member of the medical fraternity after he arrived in New Zealand was further dented by the discovery of at least two women patients who claimed to have had sex with him because, as they informed the authorities, he said he had not had sex with his wife for a long time as she had cancer. This was either fantasy or a deliberate lie, as Annette had never had cancer.

My involvement was confined to examining the medical aspects of the case, which were difficult to disentangle from the non-medical, and to express an opinion on them. If, as the defence contended, Annette's illness was genuine and happened to coincide with her husband's own planned suicide with hypoglycaemia-inducing drugs–which she discovered only after her final discharge from hospital and used to end her life–the case against him should fail, despite the undoubtedly very strong circumstantial evidence against him.

Annette had undoubtedly suffered from intractable hypoglycaemia throughout the last six weeks of her life. According to Colin's lawyer, there was evidence that Dr Geary, the Assistant Dean of the medical school where Colin worked, had suggested in September 1999 that Annette might have an insulinoma rather than the brain tumour that Colin said he suspected. No one of course knew at that stage just what a fantasist and liar Colin was, as this only really emerged in the period leading up to his trial. Colin's conversation with Dr Geary was construed as preparatory to what he proposed to do and designed to divert suspicion away from the possibility that Annette's hypoglycaemia was sulphonylurea-induced.

Whatever the motivation for this conversation, there is no doubt that Colin persuaded Annette to have a blood test on 15 November 1999, which showed that everything tested for was normal. The blood test was carried out just a day before Colin wrote his first prescription for glibenclamide and only five days before Annette had her first hypoglycaemic coma. With hindsight, Annette's hypoglycaemia was inadequately investigated. The failures included not collecting and preserving sufficient blood to undertake a sulphonylurea assay until at least 18 hours after she was first diagnosed with hypoglycaemia, and using a test so insensitive that it could only detect massive overdosing. Dr Bowers did not know this, however, as presumably the analyst never told him, and because the negative test supported Colin's assertion that there were no sulphonylureas in the house, the possibility that Annette's hypoglycaemia was factitious was dismissed from further consideration.

Professor Evan Begg, the pharmacologist consulted by the prosecution, described the lower limit of sensitivity of the assay used to measure sulphonylureas in Annette's blood sample when she first came into hospital suffering from hypoglycaemia as 176 µg/L, which would only have been capable of detecting a suicidally large dose of sulphonylureas. This assay was 300 times less sensitive than the immunoassay in use in my own laboratory at that time, which could detect sulphonylureas from as little as 0.5 µg/L – sensitive enough to detect if they are present and responsible for a patient's hypoglycaemia, however long after they have been taken.

Analysis of the last specimen of blood collected from Annette by Colin on the afternoon of her death established that sulphonylureas were, at least on that occasion, associated with her hypoglycaemia, and then only after they had been found in the postmortem specimens of blood. Although the temptation to attribute all of Annette's earlier hypoglycaemic episodes to sulphonylureas is strong, this was not established by evidence. In retrospect, neither the original sulphonylurea assay result nor Colin's word should have been relied upon. What is somewhat surprising is that despite the recurrence of her hypoglycaemia in hospital after the failure to find an insulinoma, Annette's doctors did not suspect surreptitious, perhaps self-administered. sulphonylurea use and ask for another assay.

The intra-arterial calcium infusion test result was to play a key role in the evolution of the case against Colin in court. It was unlike that seen in insulinoma patients, but remarkably like that seen in patients with a diffuse abnormality of the islets of Langerhans, the pancreatic cell clusters within the pancreas that produce insulin, as Dr Ian Holdaway, the Professor of Endocrinology in Auckland, had pointed out to Dr Manning, who had consulted him before Annette's operation. Islets do not need to appear abnormal under the microscope for them to misbehave in response to calcium as though they were insulinoma cells. Dr Yoon, who had originally dismissed the possibility that Annette's islets were enlarged, subsequently agreed that they were. The increased size of the islets was said to result largely from an increase in the number of glucagon-secreting rather than of insulin-secreting cells. This abnormality, the prosecution alleged, was further evidence of chronic sulphonylurea administration rather than a natural abnormality. This seems inherently unlikely as Annette could not have taken the sulphonylurea drugs for more than six

weeks, at most, and the scientific evidence that sulphonylureas *ever* produce islet hypertrophy is flimsy. Islet enlargement is, however, common in patients harbouring an insulinoma as well as in other conditions not associated with hypoglycaemia, and only very rarely is islet hyperplasia the primary cause of intractable hypoglycaemia.

If Colin had indeed been giving Annette sulphonylurea drugs, it is difficult to imagine how he did so whilst she was in hospital – or even at home, as she was known to abhor taking medicines of any kind. Even more mysterious is how he managed to get her to take the cocktail of drugs found in her body at autopsy. The prosecution produced evidence that a pestle and mortar they had found in the Bouwer house had been used to grind up glibenclamide and sulphapyridine (a sulphonamide antibiotic that does not produce hypoglycaemia and is only distantly related to the sulphonylureas). A plastic jar also found contained a powdered mixture of glibenclamide and sulphasalazine, another sulphonamide antibiotic, which is converted in the body into sulphapyridine.

Since neither sulphapyridine nor sulphasalazine were found in Annette's body, it is difficult to see the relevance of this discovery. Interestingly, the pestle and mortar did not contain metformin. This is so foul-tasting that it is difficult to imagine how it could have got into Annette's body in as large an amount as was found at autopsy unless she had voluntarily swallowed 30 or more tablets or they had been ground up and put down a tube inserted through her mouth into her stomach. This would only have been possible if she had been rendered unconscious by some drug or other, and there would probably have been signs around her mouth of a forced entry.

The trial itself began in Christchurch in October 2001, nearly two years after Annette's death, and lasted 6 weeks. The prosecution called 155 witnesses, of whom 11 were expert or professional witnesses. The defence called just five witnesses, of whom three, including myself, gave expert testimony. Part of the attraction for the world's media was Colin's tall stories, his larger-than-life Walter Mitty character, and the fact that his son by a previous marriage was simultaneously undergoing investigation in South Africa for murdering his own wife, for which crime he was convicted in 2003.

At one stage the court was linked by satellite television with South Africa, where the doctors who Colin said had operated on him for carcinoma of the prostate whilst he was on bail denied all knowledge of him. They also showed the court a forged letter on their hospital's headed notepaper, describing his illness and its treatment. Another witness introduced evidence that during a tutorial with his students Colin discussed insulin injection between the toes as a perfect means of committing murder. This bizarre and unrealistic suggestion also featured in both the Maria Whiston and Deborah Winzar cases in the UK,[2,3] though there was never any evidence to support the idea that it was done.

The prosecution's case was that Colin had become enamoured of Anne Walshe in September 1999 and hatched a plan to rid himself of his wife and at the same time collect a large insurance premium on her life. He had systematically poisoned her by giving her drugs that would produce hypoglycaemia and eventually, in sufficient overdose, kill her. When this failed to achieve his objective, he used insulin to finish the job. The defence case was that the prosecution had no direct evidence that, until the last days of her life, drugs were in any way implicated in her illness and that her death was caused by drugs she had taken with suicidal intent after discovering her husband's hoard. There is no doubt that she was very depressed by her continuing illness and may well have found out about Colin's affair with Anne Walshe.

Dr Peter Ellis, an Englishman who had been Director of the Department of Forensic Medicine at Westmead Hospital's Institute of Clinical Pathology and Medical Research in Sydney, Australia, was retained as an expert by the defence. With the benefit of 25 years' experience, during which time he had performed some 7000 autopsies, he said that the postmortem examination of Annette's body had been of poor quality and incapable of elucidating the cause of her death. Instead it seemed to have been performed to seek an elusive insulinoma that was never found. Dr Ellis was particularly critical of the failure to preserve Annette's brain intact for examination by a neuropathologist who could look for the telltale features that characterize hypoglycaemia. He was, in my opinion, absolutely correct in being sceptical of the abnormalities found in Annette's heart being due to hypoglycaemia and appalled by the failure to collect blood for insulin and C-peptide assay at autopsy, as without it, any charge of poisoning by insulin could be no more than conjecture. Dr Ellis concluded that there was insufficient evidence to specify the cause of Annette's death.

In my view, although there was strong circumstantial evidence that Annette's two admissions to hospital and the hypoglycaemia she suffered following her discharge on Christmas Eve 1999 were due to sulphonylureas, there was no direct evidence for this, although it could easily have been obtained if her doctors had done the relevant tests. There was also the remote possibility that her earlier episodes of hypoglycaemia were due to underlying natural illness, as the doctors treating her suspected right up to the time of her death. This was undoubtedly associated with, and almost certainly due to, the very large number and amount of drugs she had taken in the 12 hours preceding her death, though whether she had taken them voluntarily, or whether her husband had in some way forced them on her, remained for the jury to decide.

In his summing up, the judge pointed out that it was for the jury, not the experts, to decide the facts of the case. The jury must have been influenced by the coincidence of Colin's bout of improper prescription-writing for hypoglycaemia-producing drugs with the onset of Annette's illness, in which hypoglycaemia, normally a rarity, featured so prominently. Much was made by the prosecution of the number and size of the false prescriptions – the first one alone would have been sufficient to kill several people. Why, unless he was completely deranged, would Colin have accumulated sufficient glibenclamide to kill a regiment, and written prescriptions that were so easily traceable to him?

The possibility of a motive, demonstrated by defence counsel to be confined to matrimonial freedom, may also have affected the jury, but possibly the most telling point, stressed by the judge in his summing up, was the statement made by Colin to several witnesses, including Annette's mother, that Annette had a terminal illness long before this was considered, but dismissed, by her medical attendants, who never believed it. The judge in his summing up also emphasized that, on the afternoon before she died, Colin phoned his mother-in-law in South Africa to tell her that Annette was dying but not to bother to come to New Zealand, as Annette would be dead by the time she arrived.

Death from hypoglycaemia is always preventable, as the case of Paul Crampton shows,[4] and Colin's implied callousness in not taking Annette to hospital where she could have been given intravenous glucose probably did more to convince the jury of his guilt than the demonstration that he was an inveterate liar, womanizer and fantasist. Annette was, however, a very strong-minded woman and according to the defence resolutely refused to have any further treatment. The clinical and other aspects of Annette Bouwer's illness have been described the medical team looking after her.[5] Since Colin has continued to maintain his innocence, the truth about Annette's hypoglycaemia will probably never be known.

Colin Bouwer's trial in the High Court of New Zealand in Christ Church lasted from 8 October to 19 November 2001. The jury was out for 3 hours and 25 minutes and returned a guilty verdict. On the same day the Royal College of Psychiatrists of Australia and New Zealand revoked Colin's fellowship of the College. On 18 June 2002 The Court of Appeal of New Zealand dismissed an appeal launched on Colin's behalf by David More and Anne Stevens, his defence lawyers. Instead it upheld an appeal by the Solicitor-General to increase the minimum time that Colin should serve in prison from 13 to 15 years of a mandatory life sentence imposed on him by the trial judge on account of the heinousness of his crime.

References

1 Marks V. Murder by insulin. *Medico-Legal Journal* 1999;**67**:147–63

2 Marks V, Richmond C. Maria Whiston, England: the 'insulin between the toes' case. In: *Insulin Murders.* London: RSM Press; 2007. p. 81–94

3 Marks V, Richmond C. Deborah Winzar, England: a case of wrongful conviction? In: *Insulin Murders.* London: RSM Press; 2007. p. 103–32

4 Marks V, Richmond C. Beverly Allitt, England: the nurse who killed babies. In: *Insulin Murders.* London: RSM Press; 2007. p. 55–74

5 Mnning PJ, Espinert EA, Yoon K, Drury PL, Holdaway M, Bowers A. An unusual cause of hyperinsulinaemic hypoglycaemia. *Diabetic Med* 2003;**20**:772–6